REMARKS/ARGUMENTS

Reexamination and reconsideration of this Application, withdrawal of the rejection, and formal notification of the allowability of all claims as now presented are earnestly solicited in light of the above amendments and remarks that follow. Claims 2, 3, 12-21, and 35-38 are pending in the application. Claim 19 has been amended as suggested by the Examiner to correct a minor antecedent basis error. Applicants respectfully submit that no new matter is introduced by this amendment.

Claim 19 stands rejected under 35 U.S.C. §112, second paragraph, as being indefinite. In particular, the Examiner notes that the term "plasticizing substance" does not have antecedent basis in claim 2. In response, Applicants have amended claim 19 to refer to a cellulose derivative. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection.

All claims stand rejected under 35 U.S.C. §103(a) as being unpatentable over the previously-cited O'Leary *et al.* patent in view of the previously-cited Yim *et al.* patent, U.S. Patent No. 5,366,507 to Sottosanti, U.S. Patent No. 4,619,655 to Hanker *et al.*, U.S. Patent No. 5,425,769 to Snyders, Jr., and WO 98/40113 to Wironen *et al.* Claims 2, 3, and 12-21 also stand rejected as unpatentable over the above-noted combination of references, and further in view of the Gertzman *et al.* patent. In making this rejection, the Examiner relies upon the O'Leary reference as describing a composition comprising demineralized bone powder in a biocompatible liquid synthetic organic material as a carrier and, optionally, a thixotropic agent. The Examiner appears to rely on the combined teachings of Yim, Sottosanti, Hanker, and Snyders, Jr. as suggestive of adding calcium sulfate to the formulation of O'Leary. In support of this contention, the Examiner points to a suggestion in Yim that calcium sulfate hemihydrate improves osteoconduction. The Examiner also points to teachings in Sotosanti, Hanker, and Snyder, Jr. regarding the use of calcium sulfate hemihydrate in various bone graft composite materials and concludes that these references would motivate one to modify the O'Leary reference by the addition of calcium sulfate in order to improve the osteoconductive properties of the final material. Applicants respectfully traverse these rejections.

In the opinion of Applicants' representative, the Examiner's new rejection is merely a rehashing of arguments already presented to the Board and overruled. In particular, Applicants' representative is dismayed by the continued reliance of the Examiner on a combination of the O'Leary and Yim references. This is particularly troubling when the Board of Appeals has already ruled that the combination of O'Leary and Yim would not motivate one of ordinary skill in the art to add calcium sulfate hemihydrate to the O'Leary formulation. In reaching this determination, it is also noted that the majority decision by the Board has already expressly considered the teachings in Yim regarding the osteoconductive properties of calcium sulfate hemihydrate-containing substances (see BPAI opinion, page 9, last paragraph). In the very next paragraph after the Board specifically mentions the Yim teaching regarding the osteoconductive properties of calcium sulfate hemihydrate-containing substances, the Board states: "[t]his reasoning relies on the hindsight reconstruction that the courts have condemned." The Board goes onto state that the cited references, when viewed without the benefit of Applicants' disclosure, essentially teach different approaches to solving the same problem, the problem being "making a composition that can be put (and will stay) in a bone defect and promote growth of new bone" (see BPAI opinion, page 10). The Board goes further to state that each of the prior art compositions and the cited art disclose a complete bone graft substitute composition having bone growth promoting properties. As noted by the Board, none of the compositions are likely perfect, and each of them could have been further modified. However, in the Board's view, when "viewed without the benefit of hindsight, the references would not have suggested modifying the prior art compositions in a way that would produce the composition claimed here." (BPAI opinion, page 10). Despite this very clear language in the Board decision, the main motivation for combination relied upon by the Examiner continues to be based on teachings in the art regarding the osteoconductive nature of calcium sulfate hemihydrate. Perhaps realizing that the Board has already dismissed this particular line of reasoning, the Examiner attempts to bolster the argument by cobbling together three additional references that are similarly irrelevant to the O'Leary formulation, but nevertheless describe a previous use of calcium sulfate hemihydrate in a bone graft material.

It is respectfully noted that Applicants are not attempting to claim invention of the first

use of calcium sulfate hemihydrate in bone graft materials. Further, the claims of record are not so all-encompassing. Instead, the claimed invention is directed to a composition that includes calcium sulfate, a mixing solution, a cellulose derivative, and demineralized bone. Despite the Examiner's protestations that all of these ingredients are common in bone graft compositions, not one single reference has been shown that suggests combinations of all these ingredients in a single composition.

The Snyders, Jr., Sottosanti, and Hanker references add nothing to the previous rejection based only on O'Leary and Yim. As with Yim, as noted by the Examiner, these references also teach that calcium sulfate hemihydrate can have osteoconductive properties. However, as noted above, the Yim reference already discloses such properties and the Board has already considered such a teaching as failing to provide the necessary motivation for modifying the O'Leary formulation. So as an initial matter, Applicants respectfully request reconsideration and withdrawal of this rejection for the simple reason that the logic relied upon as underpinning the rejection has already been addressed by the Board and rejected.

Additionally, there is also no motivation to modify the O'Leary formulation as suggested in this rejection because the O'Leary reference is directed to a "flowable" composition and particularly states that the object of the O'Leary invention is to provide "a composition of liquid or paste-like consistency" and to apply "the composition" to a bone defect site to induce new bone growth (column 1, lines 36-43). The O'Leary disclosure also states that the bone powder composition described therein can be prepared beforehand and stored in a sterile condition for later use, and even stored within the syringe or other means for applying the composition (column 1, lines 63-67; column 4, lines 34-37). Applicants respectfully submit that the Examiner has not adequately explained how one of ordinary skill in the art would be motivated to overlook this clear requirement in O'Leary by adding a substance known to cause hardening (i.e., negate flowability) of a composition.

It is quite well-known in the art, including in the references cited by the Examiner, that calcium sulfate hemihydrate hardens into a plaster upon reaction with water. For example, the Yim reference itself describes how quickly calcium sulfate hemihydrate solution loses flowability in Table 2 in column 10. Note that each tested composition appearing in Table 2 was

non-flowable within 15 minutes. Better evidence against the combination of O'Leary and Yim could hardly be imagined. Similarly, the Hanker patent specifically notes that the plaster of paris-containing composites described therein can be preformed into a desired shape, which obviously implies that the composition when mixed will harden into a desired shape that can then be inserted into an implant (column 2, lines 42-45). Sottosanti also recognizes the very well-known hardening properties of calcium sulfate hemihydrate, noting that the calcium sulfate paste sets and hardens to create a physical barrier (column 3, lines 55-59). The Snyders, Jr. patent also evidences an understanding of this property of calcium sulfate hemihydrate, by noting that the composition described therein is designed to mimic the structure of human bone, referencing setting time in Table I, and referring to a rapid *in vivo* set in Example I. Additionally, claim 1 of the Snyders, Jr. patent clearly discloses that the material described therein is molded *in situ* from a pliable phase to a solid phase when implanted.

All of these references make it clear that those of skill in the art understand the hardening/setting properties of calcium sulfate hemihydrate. The Examiner has failed to explain why one of ordinary skill in the art would be motivated to modify the O'Leary formulation with an additional component that is known to cause formulations to harden into a non-flowable state. As relevant case law makes clear, a proposed modification of the prior art cannot render the prior art unsatisfactory for its intended purpose or change the principle of operation of the primary reference. See MPEP 2143.01, Subheadings V and VI. The present rejection could be viewed as running afoul of either rule. One of ordinary skill in the art would view the addition of calcium sulfate hemihydrate as rendering the O'Leary composition unsatisfactory for the intended purpose of providing a flowable composition that can be prepared well in advance of use and stored. Further, one of ordinary skill in the art would view the addition of calcium sulfate hemihydrate to the O'Leary composition as violating a basic principle of operation (i.e., flowability) for which the O'Leary composition is designed. For this additional reason, Applicants respectfully request reconsideration and withdrawal of all rejections based on a combination of O'Leary with other references of record that describe use of calcium sulfate hemihydrate.

It is noted that the Office Action provides an alternate view of the prior art where the art

is viewed as suggestive of not simply adding calcium sulfate hemihydrate to the O'Leary formulation; but rather, replacing the glycerol or similar carrier with calcium sulfate. Applicants also specifically traverse this line of reasoning as it cannot be viewed as properly motivated by the art and would obviously result in a composition that does not meet the basic flowability requirements of the O'Leary reference as noted above.

The O'Leary reference essentially teaches a composition comprising demineralized bone in a biocompatible liquid synthetic organic material as a carrier. Glycerol is described as a particular preferred carrier. The Examiner reasons that because the Wironen reference raises questions about the advisability of using glycerol, one of skill in the art would be motivated to replace such an ingredient with calcium sulfate as a carrier/scaffold. As an initial matter, the problem with this line of reasoning is the same as noted above regarding the requirement in O'Leary that the composition be flowable. Calcium sulfate hemihydrate, when mixed with water, is known to form a hardened mass in a relatively short period of time. See, for example, Table 2 in column 2 of the Yim reference. Again, as noted above, there is a prohibition against basing obviousness rejections on modifications that would result in the prior art composition being unsatisfactory for its intended purpose or that would change the principle of operation of the reference. Clearly, removing the carrier component of O'Leary and replacing it with calcium sulfate hemihydrate, an ingredient known to form a hardened mass when mixed with water, would radically change the theory of operation of the O'Leary formulation and would not provide a flowable composition, which is one of the basic requirements noted in the O'Leary patent.

Notwithstanding the foregoing, even if one of skill in the art were motivated to replace the flowable carrier of O'Leary with calcium sulfate hemihydrate, the resulting combination would still not result in Applicants' claimed invention. All claims of record also recite the presence of a cellulose derivative. As noted by the Examiner, the O'Leary reference classifies certain cellulosic materials as thixotropic ingredients that can be useful to prevent bone powder from prematurely separating from the carrier (i.e., settling out from the composition). In particular, the O'Leary patent notes that when the carrier component is glycerol, a thickener can be used to improve the suspension properties of the composition. If the Examiner's logic holds

true, then removal of the glycerol-type carrier will also remove the necessity of a thixotropic ingredient. There is certainly no need for additional ingredients to keep powders in "suspension" when utilizing calcium sulfate hemihydrate as the primary carrier ingredient. When a composition is intended to form a hardened mass in a short period of time, settling of powder is not an issue. This is likely why you do not see any reference to thixotropic ingredients in any of the remaining references of record that utilize calcium sulfate hemihydrate. Thus, even if the Examiner's reasoning is accurate, which Applicants do not admit, the resulting combination would still not result in the claimed invention. For these additional reasons, Applicants also respectfully request reconsideration and withdrawal of any rejections based on the "replacement" theory set forth in the Office Action.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

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